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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,992	12/19/2001	David Bebbington	VPI/00-130-4	2621

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/026,992	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11, 14, 16-17, 20, 22-25, 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14,16,17,20,22-25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20060228
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on February 28, 2006.

Claims 1-11, 14, 16-17, 20, 22-25 and 27 are pending in this application.

The following rejections are maintained:

1. Claims 11, 23-25 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of colon cancer, does not reasonably provide enablement for the treatment of all other diseases embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'claims 11 and 23-25 do not relate to the treatment of any recited diseases'. Claim 11 is drawn to a method of inhibiting Aurora-2, GSK-3, or Src in a biological sample' and the term "biological sample" is defined in the specification (page 24, lines 5-10) to 'include, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof'. As can be seen from the definition of the term, without limitation it reads on many types of biological samples, including mammals or animals and therefore, they are seen to encompass methods wherein the compound is administered to an animal.

Claims 23-25 are drawn to a method of enhancing glycogen synthesis or lowering blood

levels of glucose in a patient; a method of inhibiting the production of hyperphosphorylated Tau protein; or a method of inhibiting the phosphorylation of β-catenin, respectively, without specifically identifying a disease state or condition and therefore include any or all types of disease states that are associated with the recited mechanism. The instant claim appears to be a 'reach through' claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention. Further, there is nothing in the specification or the state of the art to provide how this particular enzymatic pathway correlates to the treatment of various diseases of the instant claims having diverse mechanisms involving various organs of the human body.

With regards to claim 27, applicant argues that 'the cited references link Src with the recited disorders'. Applicant appears to rely on Soriano et al., Weiner et al., and Staley et al., to provide the link between Src and the claimed disorders of 'hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, or paget's disease'. First, copies of the above references are not made available for consideration. Next, as submitted by applicant, each of the reference appears to provide link between Src and a specific disorder, i.e., Soriano (osteoporosis) and Weiner and Staley (colon tumor). The references do not appear to provide enablement for the scope of the instant claim reciting a method of treatment of assorted diseases including "cancer". The state of the art does not provide how the data disclosed in the specification can be extrapolated to the treatment of all types of diseases related to the Src biochemical pathways recited in the instant claims, and the diseases having diverse etiologies -

hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, or paget's disease. While the specification provides sufficient enabling disclosure for the synthesis of the instantly claimed compounds, does not provide an enabling disclosure sufficient to cover the entire scope of the methods of use recited in the instant claims.

Claim 27 continues to recite 'a method of treatment of cancer'. As indicated in the previous office action, a 'cancer' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

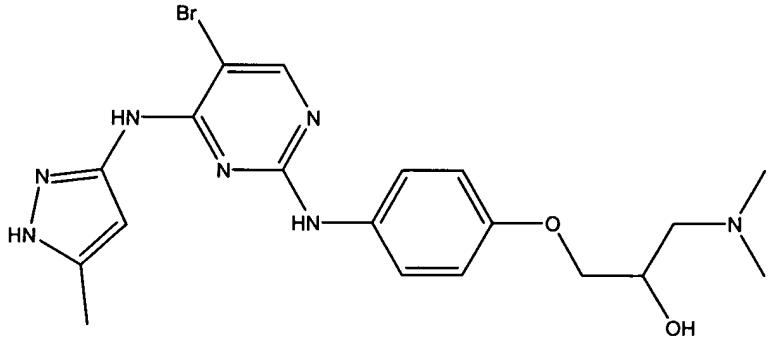
Applicant has not provided sufficient evidence that establishes that the disclosure would

have enabled for one skilled in the art at the time of filing. Further, the state of the art does not identify a single class of compounds that can treat all types of diseases of the instant claims. Further, one skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the Aurora-2, GSK-3 and Src kinases, alongside the elucidation of the molecular pathology of individual diseases is required to identify disease types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support the method of inhibition or treatment commensurate in scope with the claims, as of the filing date of the application.

2. Claims 1-11, 14, 16-17, 20, 22-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al., WO 00/39101 **or** Armistead et al., WO 01/60816 **or** Pease et al., WO 01/64655. The reasons provided in the previous office action are incorporated hereby reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant cites MPEP § 2143 and argues that 'to establish a prima facie case of

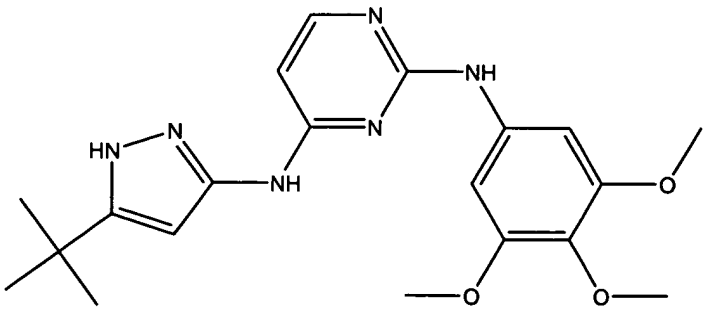
obviousness, there must be some suggestion or motivation; reasonable expectation of success; and the prior must teach or suggest all the claim limitation'. As indicated in the previous office action, all of the above conditions required to establish a prima facie case of obviousness have been met. The references individually teach pyrazolyl substituted pyrimidine compounds, which are disclosed, to have kinase inhibitory activity. See, for example, WO 00/39101 formula I in page 2 and the species of Example 135 (depicted below for convenience):



1-[4-[[5-bromo-4-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyrimidinyl]amino]phenoxy]-3-(dimethylamino)-2-propanol

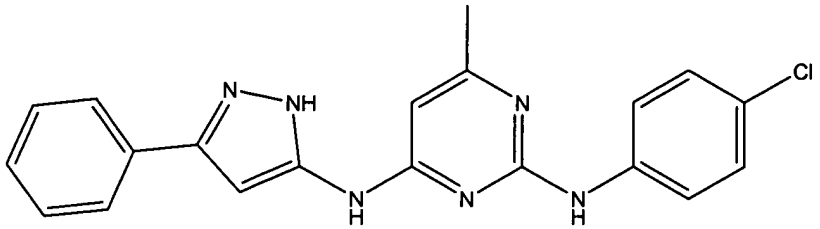
The instant claim on the other hand recite that the substituent at the 6-position (R^y) can be a halo, e.g., bromo, while the substituent at the 5-position (R^x) can be hydrogen. Therefore, the instantly claimed compounds differ from the reference compounds by the position of the substituent and are therefore, positional isomers.

Similarly, WO 01/60816 discloses a compound (depicted below for convenience):



N4-[5-(1,1dimethylethyl)-1H-pyrazol-3-yl]-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine

The instant claims differ from the above compound by having a substituent (R^y) which can be a C_{1-6} aliphatic group, e.g., a methyl group. See, for example, claim 8, the eleventh compound (page 9, lines 11-12) (depicted below for convenience):



[2-(4-chlorophenyl)amino-6-methyl-pyrimidin-4-yl]-(5-phenyl-2H-pyrazol-3-yl)-amine

Therefore, the instantly claimed compounds differ from the reference compounds by a $-CH_2$ group and are therefore, structural homologs of the reference compounds.

In other words, the instant claims differ from the reference compounds as being structural isomers or homologs. It has been held that compounds that are structurally analogous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results.

The reference compounds are taught to be useful as pharmaceutical agents having kinase inhibitory activity, which is the same use recited for the instant claims. "When chemical compounds have 'very close' structural similarities, without more a *prima facie* case may be made", see *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologs and structural isomers). "When such 'close' structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forwards shifts to the applicant, and evidence affirmatively supporting unobviousness is required", *In re Grabiak*, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985). Thus, case law supports the position that a claimed chemical compound suggests a positional isomer thereof (i.e., structurally analogous compounds differing from the reference compounds by the position of substituent); or a structural homolog

thereof (i.e., a structurally analogous compounds differing from the reference compound by a –CH_2 group) and therefore renders those positional isomers or structural homologs *prima facie* obvious.

"An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). Reference must be considered under 35 U.S.C. 103, not only for what it expressly teaches but also for what it fairly suggests, in determining obviousness. *In re Burckel*, 201 USPQ 67 (CCPA 1979). If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compounds from the prior art. The reference teaches a use for the compounds, which is sufficient to one of ordinary skill to make the claimed compounds because similar properties are normally presumed when compounds are very close in structure.

Contrary to applicant's arguments based on MPEP 2143.01, each of the references, **individually** taught and disclosed compounds that are structurally analogous to the instantly claimed compounds, see the structures depicted above. "Structural relationships provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." See *In re Duel*, 51 F.3d at 1558, 34 USPQ2d at 1214. The closer the physical and chemical similarities between the claimed species or subgenus and any exemplary species or subgenus disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner to the genus. See *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904.

It is maintained that one of ordinary skill in the art would have been motivated to pre pare the instantly claimed compounds that differ from the reference compounds by having a hydrogen in place of the methyl, with the reasonable expectation that such structurally analogous compounds would have similar properties and therefore, the same use as taught for the reference compounds, in the absence of a showing to the contrary.

The following rejections are necessitated by the amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 depends from a canceled claim (claim 21).

Receipt is acknowledged of the Information Disclosure Statement filed on February 28, 2006 and a copy is enclosed herewith.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

May 30, 2006